Benzoquinone Imines. Part 18.[1] Kinetics and Mechanism of Oxidative Coupling Reactions involving *N,N*-Bis-(2-hydroxyethyl)-*p*-phenylenediamine

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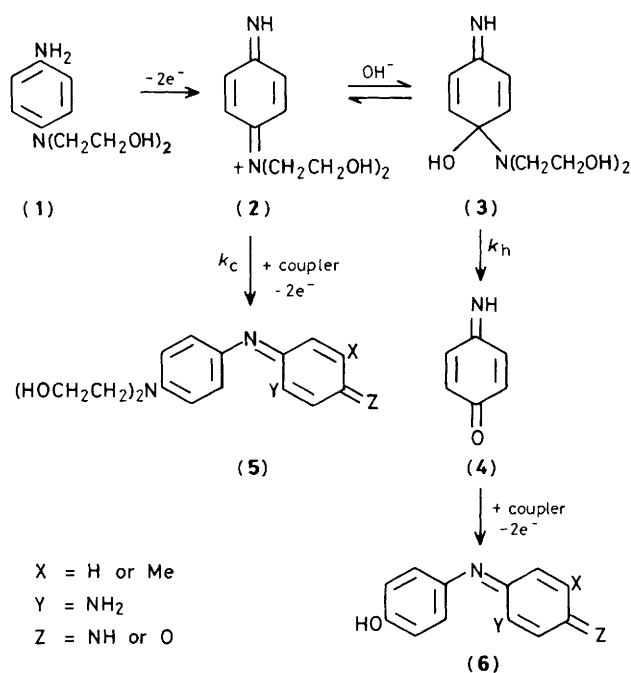*Clairol Research Laboratory, 2 Blachley Road, Stamford, Connecticut 06902, U.S.A.*

A kinetic and mechanistic study of oxidative coupling reactions of *N,N*-bis-(2-hydroxyethyl)-*p*-phenylenediamine with *m*-phenylenediamines, phenols, and acetoacetanilide is described. The reactions involve the rapid establishment of an equilibrium between *N,N*-bis-(2-hydroxyethyl)-*p*-benzoquinone di-imine and a hydroxy-amine intermediate (**3**). Competition between direct coupling of *N,N*-bis-(2-hydroxyethyl)-*p*-benzoquinone di-imine and hydrolysis to *p*-benzoquinone monoimine *via* (**3**) with subsequent coupling leads to a mixture of two dye products. The relative yields are dependent on pH and coupler concentration. Kinetic evidence for the formation of the intermediate (**3**) is presented.

Earlier parts in this series described dye-forming oxidative coupling reactions of *p*-phenylenediamines and *p*-amino-phenols.[2-6] We now extend this work with a study of coupling reactions involving *N,N*-bis-(2-hydroxyethyl)-*p*-phenyl-enediamine (**1**), an important derivative of *p*-phenylenediamine used in the hair dye industry. Reactions of the parent *p*-phenylenediamine involve initial oxidation to *p*-benzoquinone di-imine, followed by rate-determining reaction of the conjugate acid of the di-imine with either the anionic form of a phenol coupler or the neutral form of a *m*-diamine coupler.[3] *N,N*-Bis-(2-hydroxyethyl)-*p*-benzoquinone di-imine (**2**) [the fully oxidized form of (**1**)] has no ionizable proton and is therefore expected to exist exclusively as the reactive cationic form at all pH values. Thus, if oxidative coupling reactions of (**1**) followed the mechanism established for *p*-phenylenediamine, the observed rate constants at basic pH should be many orders of magnitude greater than those of *p*-phenylenediamine (pK_a of protonated *p*-benzoquinone di-imine 5.75[3b]). Furthermore, the pH-dependence of the second-order rate constants should simply reflect coupler ionization and therefore be invariant with pH for reactions involving *m*-diamines (which have no ionization in the pH range of interest), and be proportional to phenolate concentration for reactions involving phenol couplers.

The present study of the reactions of (**1**) with the couplers *m*-phenylenediamine (MPD), 4-methyl-1,3-phenylenediamine (MTD), *m*-aminophenol (MAP), 2,6-dimethylphenol (DMP), phenol, *o*-cresol, and acetoacetanilide (AAA) between pH 8.0 and 12.5 reveals that the forms of the pH–rate profiles are not as expected. A modified mechanism which accounts for the observations is proposed.

Results and Discussion

In order to investigate the kinetics of the coupling step, it is necessary to generate the di-imine (**2**) *in situ*, both quantitatively and rapidly, relative to the subsequent reactions of interest. Potassium hexacyanoferrate(III) has previously been used for this purpose in studies of coupling reactions of *p*-phenyl-enediamine[3,5,7] and hydrolytic deamination of (**1**).[8] We have established that hexacyanoferrate(III) is also a suitable reagent in coupling reactions of (**1**). Rates of oxidation of (**1**), determined by monitoring the decrease in absorbance at 420 nm caused by hexacyanoferrate(III) reduction, were always at least 20 times greater than the observed rates of dye formation under the same

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X = H or Me
Y = NH₂
Z = NH or O

conditions. The rate of oxidation increased with pH and became too fast to be measured by stopped flow above pH 9.5.

Hydrolysis of N,N-*Bis-(2-hydroxyethyl)-*p*-phenylenediamine* (**1**).—Tong reported that the rate constants for alkaline hydrolysis of *p*-benzoquinone di-imine show a first-order dependence on hydroxide ion concentration whereas for the di-imine (**2**), a biphasic dependence of k_{obs} on pH is observed. Levelling off of rate at higher pH in the case of the di-imine (**2**) was explained by a mechanism involving reaction between hydroxide ion and di-imine to form an intermediate (**3**), in a rapid pre-equilibrium, with levelling off occurring as the intermediate–di-imine ratio became large. It was suggested that hydrogen bonding by the hydroxyethyl group gives the intermediate stability not available to the parent di-imine.

We have confirmed Tong's observation of a levelling off in rate with the di-imine (**2**). The increase in absorbance at 250 nm, after mixing hexacyanoferrate(III) (1×10^{-4}M) and (**1**) (5×10^{-5}M) in various buffers at 30 °C was monitored by stopped flow. It was found that the hydrolysis involves a previously unobserved initial fast step followed by a slow step. At pH 8.4 a rate constant of 33.0 s⁻¹ was determined for the fast

Table 1. Stoicheiometry of reactions of N,N-bis-(2-hydroxyethyl)-p-phenylenediamine with various couplers at pH 8. Concentrations for MTD and MAP are multiples of 5×10^{-5}M; concentrations for o-cresol are multiples of 8.2×10^{-5}M; concentrations for AAA are multiples of 9×10^{-5}M

Reactant concentrations			Maximum absorbance			
[(1)]	[coupler]	[Fe(CN)₆]	MTD 636 nm	MAP 580 nm	o-Cresol 616 nm	AAA 452 nm
1	1	2	0.61	0.38	0.81	0.64
1	1	4	1.16	0.72	1.60	1.18
2	1	4	1.25	0.72	1.62	1.06
1	2	2	0.65	0.36	0.80	0.66

step. A limiting rate constant of 0.12 s^{-1} was obtained for the slow step (cf. Tong's value of 0.08 s^{-1} at 25 °C). By running stopped-flow experiments at various wavelengths and measuring the absorbance at the end of the fast stage, $\lambda_{max.}$ for the transient species was found to be 310 nm. The magnitude of the transient absorbance at 310 nm decreased with pH between pH 7.5 and 9.5, and the fast step is therefore thought to be formation of the di-imine in equilibrium with the base (3), which is transparent at 310 nm.[8] The slow step represents hydrolysis to p-benzoquinone monoimine.

Coupling with m-*Diamines and Phenols.—Stoicheiometry and product structure.* In principle, compound (1) can couple either at the unsubstituted nitrogen, in which case 4 mol equiv. of hexacyanoferrate(III) would be consumed in dye formation, or at the bis-substituted nitrogen, when, because the second oxidation step is not possible, only 2 mol equiv. of hexacyanoferrate(III) would be consumed.

Table 1 gives representative examples of the yield of dye obtained when compound (1), coupler, and hexacyanoferrate(III) are mixed in various ratios at pH 8. The results indicate that, as in the case with p-phenylenediamine,[3] 4 equiv. of hexacyanoferrate(III) are required in coupling reactions of (1). By analogy with p-phenylenediamine, the products of coupling reactions of the di-imine (2) are formulated as (5). Aqueous solutions of the MAP-, phenol-, o-cresol-, and DMP-derived products have $\lambda_{max.}$ (log ε) values of 580 (4.16), 630 (4.34), 616 (4.29), and 599 nm (4.23), respectively, at basic pH. The MPD- and MTD-derived products have respective pK_a values of 11.3 and 11.1, with $\lambda_{max.}$ (log ε) values of 633 (4.38) and 636 nm (4.25) for the cationic forms and 525 (4.02) and 523 nm (3.92) for the neutral forms.

The structure (5; X = H, Y = NH$_2$, Z = NH) of the dye formed in solution by reaction of (1) with MPD was confirmed by comparison of its visible spectrum with that obtained following oxidation of an authentic sample of 4'-bis-(2-hydroxy-ethylamino)-2,4-diaminodiphenylamine in solution.

Product ratios. The rapid alkaline hydrolysis of the di-imine (2) raises the possibility that dyes might be formed upon reaction of added coupler with both (2) and its hydrolysis product, p-benzoquinone monoimine. Unfortunately, dyes formed by both these pathways absorb similarly at basic pH, making it impossible to separate the reactions directly by visible spectrophotometry. However, at pH 6, products derived from the di-imine (2) absorb strongly above 600 nm, whereas the p-benzoquinone monoimine-derived products do not absorb significantly at these wavelengths. The products formed by reaction with MPD serve as representative examples: the dye derived from the di-imine (2) has $\lambda_{max.}$ 633 nm at pH 6 and in base while the p-benzoquinone monoimine-derived dye, formed in oxidative coupling reactions of p-aminophenol (PAP) with MPD, has $\lambda_{max.}$ 490 nm at pH 6 and $\lambda_{max.}$ 633 nm in base.[2]
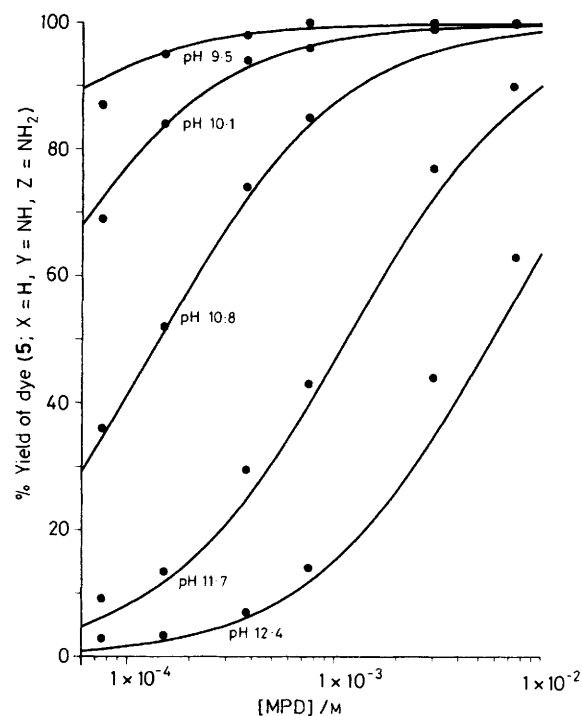

Figure 1. Percentage yields of (5; X = H, Y = NH, Z = NH$_2$) obtained in oxidative coupling reactions of N,N-bis-(2-hydroxyethyl)-p-phenylenediamine (7.5×10^{-5}M) with MPD at various pH values *vs.* MPD concentration. The lines are calculated using equation (3), $k_c = 4 \times 10^5$ dm^3 mol^{-1} s^{-1}, $k_h = 0.12$ s^{-1}

The following experiments show that hydrolysis of the di-imine (2) to p-benzoquinone monoimine, with subsequent coupling, does indeed compete with direct coupling of the di-imine under certain conditions.

Addition of 4 mol equiv. of potassium hexacyanoferrate(III) to freshly prepared buffered reaction solutions containing equimolar concentrations of (1) and MPD results in the formation of an intense blue colour ($\lambda_{max.}$ 633 nm) at all pH values between 9.5 and 12.4. However, if the pH of these reaction solutions is adjusted to 6, $\lambda_{max.}$ of the resultant solutions ranges from 633 nm (for the lowest reaction pH solution) to 490 nm (for the highest). If the experiment is repeated with increasing concentrations of MPD, the range of reaction pH values which retain $\lambda_{max.}$ 633 nm after adjustment to pH 6 increases. This implies that a greater amount of the species with $\lambda_{max.}$ 490 nm at pH 6 (the p-benzoquinone monoimine-derived product) is formed at higher pH and lower coupler–(1) ratio. In other words, high pH and low coupler concentration allow hydrolysis of the di-imine (2) to compete with direct coupling. Relative yields of the two dyes were determined in the following way. The concentration of the di-imine-derived product was determined from its extinction coefficient (calculated from data on reaction solutions at a suitable pH and with sufficient coupler present to ensure 100% conversion into di-imine dye) and the absorbance of the reaction solution above 600 nm, after adjustment to pH 6 with phthalate buffer, and making up to known volume with water. Simple subtraction from the known initial concentration of (1) gave the concentration of the monoimine dye. The validity of the calculation was confirmed by the good agreement between the observed absorbance at 500 nm and that calculated from the product ratio and the extinction coefficients of the two dyes at this wavelength. Extinction coefficients for the monoimine-

Table 2. Kinetic constants for the oxidative coupling reactions of N,N-bis-(2-hydroxyethyl)-p-phenylenediamine with various couplers at 30 °C, $I = 0.2$

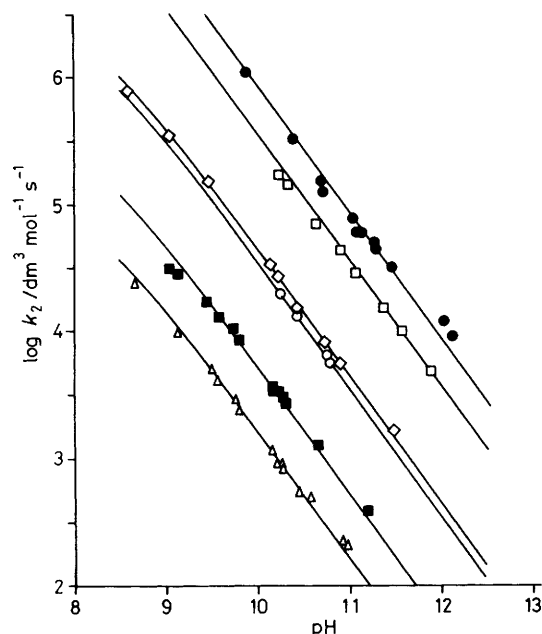| Coupler	pK_a	$k_c = k_{obs}/[c]_R$ α (dm³ mol⁻¹ s⁻¹)
m-Phenylenediamine		4.00×10^5
m-Aminophenol	10.06	2.80×10^7
4-Methyl-1,3-phenylenediamine		2.70×10^6
2,6-Dimethylphenol	10.62	6.50×10^7
Phenol	9.97	1.25×10^5
o-Cresol	10.27	3.40×10^6

Figure 2. Apparent second-order rate constants (k_2) vs. pH for oxidative coupling reactions of (1) with DMP (●), MAP (□), o-cresol (◇), MTD (○), MPD (■), and phenol (△). Data were obtained under conditions where no hydrolysis of (1) occurs. The lines are calculated from equation (2) and the data in Table 2

Figure 3. Plot of log k_c for oxidative coupling reactions of N,N-bis-(2-hydroxyethyl)-p-phenylenediamine (1) with various couplers vs. log k_c for the analogous reactions of p-phenylenediamine (PPD). Regression analysis yields a value of 0.89 ± 0.18 (error limits twice the standard error) for the gradient; $r = 0.9803$

Kinetics and mechanism of coupling. As expected, the observed rates for coupling reactions of compound (1) are rapid relative to those of p-phenylenediamine. Figure 2 shows plots of k_{obs} vs. pH of the reaction mixture. The lines are calculated from equation (2) and the data in Table 2. The unexpected form of these pH–rate profiles can be accounted for by a mechanism incorporating the intermediate (3) proposed by Tong.[8]

Like p-phenylenediamine, coupling reactions of (1) involve rate-determining reaction between free di-imine (2) and either the anionic form of a phenolic coupler or the neutral form of a m-diamine coupler. The rate of di-imine-derived dye formation is then given by equation (1), where k_c is the pH-independent rate

$$d[(5)]/dt = k_c \, \alpha \, [(1)]_T \, [C]_R \qquad (1)$$

constant for coupling, α is the fraction of (1) present as (2), $[(1)]_T$ is the initial concentration of (1), and $[C]_R$ is the concentration of the reactive form of the coupler. Thus, $k_{obs} = k_c \, \alpha \, [C]_R$, giving equation (2). The lines in Figure 2 are drawn using

$$k_2 = k_{obs}/[C]_R = k_c \, \alpha \qquad (2)$$

equation (2), the values of k_c in Table 2, and an equilibrium constant $K = [(3)]/[(2)][OH^-] = 7.6 \times 10^5 M^{-1}$ for the rapid pre-equilibrium between (2) and (3).[8] At sufficiently high pH or low coupler concentration, the coupling pathway (k_c) and hydrolysis pathway (k_h) compete for (2), and dyes are formed from both (2) and monoimine (4). The relative yield of each dye is given by equation (3). The lines in Figure 1 are calculated by

derived dyes were obtained from reactions of PAP with the various couplers.

Figure 1 shows the effect of pH and coupler–(1) ratio on experimentally determined product yields, using MPD as an example of a typical coupler. The lines are calculated from equation (3) (see later). It is apparent that high pH and low coupler–(1) ratios favour formation of the monoimine-derived product (6). Qualitatively similar results were obtained with other couplers. Thus, oxidative coupling reactions of (1) result in dyes derived either *via* the di-imine (2) or *via* its hydrolysis product, p-benzoquinone monoimine (4).

Kinetic confirmation for this interpretation is obtained from the following experiment. When compound (1) (9.55×10^{-5}M) is oxidized with hexacyanoferrate(III) (1.91×10^{-4}M; 2 mol equiv.) and kept at pH 10.1 for 2 min before adding MPD (3.82×10^{-4}M) and 2 further mol equiv. of hexacyanoferrate(III), the rate of colour development is identical with that in a run at the same pH in which PAP (9.55×10^{-5}M) is coupled with MPD (3.82×10^{-4}M) using 4 mol equiv. of hexacyanoferrate(III) (3.82×10^{-4}M). The spectral characteristics of the products from the two reactions are also identical, indicating that compound (1), after oxidation to the di-imine, is hydrolysed to the monoimine prior to reaction with MPD.
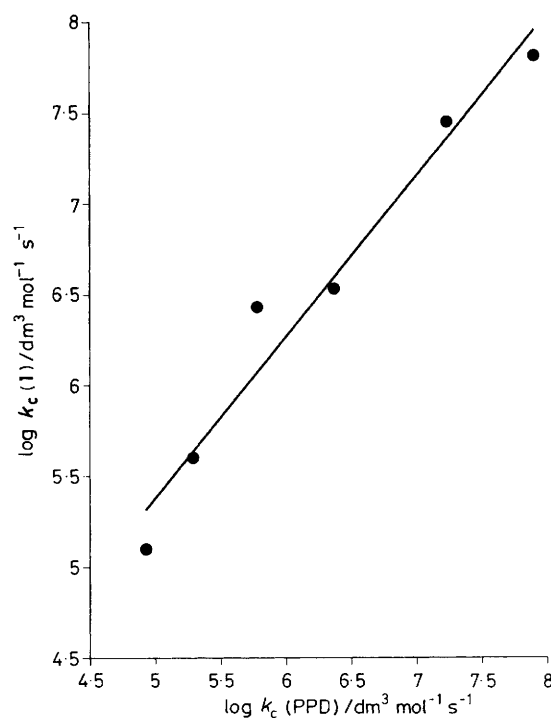
$$[(5)]/[(6)] = k_c \, \alpha \, [(1)]_T \, [C]_R/k_h[(3)] \qquad (3)$$

using equation (3).

Figure 3 shows the relationship between log k_c values for

oxidative coupling reactions of p-phenylenediamine and (1). The reasonable fit to a straight line supports the similarity of mechanism, provided account is taken of the existence of the hydrolysis pathway of the di-imine (2). The gradient of the line is not significantly different from unity, indicating similar selectivity towards couplers, as might be expected for substrates of approximately equal reactivity.

Coupling with Acetoacetanilide.—Compound (1) reacts with acetoacetanilide in the presence of an oxidant to form a yellow dye ($\lambda_{max.}$ 452 nm, log ε 4.12 at neutral pH in water). By varying the relative proportions of (1), acetoacetanilide, and potassium hexacyanoferrate(III), reaction stoicheiometry of 1:1:4 was determined (Table 1). The dependence of the pseudo-first-order rate constants for dye formation on pH is described by the rate law (4), where [AAA⁻] represents the concentration of

$$k_{obs} = 5.5 \times 10^6 \, [AAA^-] \, \alpha \qquad (4)$$

acetoacetanilide as its free base (pK_a of CH_2 group 10.57, determined spectrophotometrically at 294 nm). By analogy with the reaction of p-phenylenediamines with benzoylacetanilides,[9] the product of the reaction is formulated as (7).

(7)
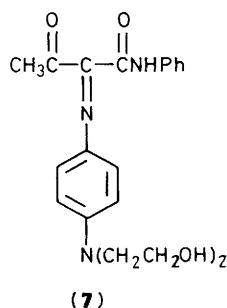
Experimental

Kinetics.—Kinetic experiments were performed with a Durrum Rapid Kinetics Systems Series D100 stopped-flow instrument; data collection and treatment were carried out with a Northstar Horizon computer using software supplied by OLIS.[10] Coupling reactions were run under pseudo-first-order conditions (large excess of coupler) at coupler concentrations and pH values where 100% yields of the di-imine dye were obtained. Reactions were initiated by mixing, from one syringe, a solution of (1) and the coupler, and from the other, a solution of potassium hexacyanoferrate(III) at a molar concentration four times that of (1). The (1)–coupler solutions were prepared from stock solutions of the two reagents immediately prior to use. Stock solutions were kept for no longer than 4 h. Reactions were monitored at the product $\lambda_{max.}$ values. All runs were at 30 °C in potassium hydroxide, 0.05M- or 0.025M-phosphate, 0.05M-borate, or 0.025M-carbonate buffer maintained at ionic strength 0.2 with KCl. No evidence of buffer catalysis was found.

Concentrations of (1) were generally between 5×10^{-5} and 1×10^{-4}M. Rate constants were routinely determined from 'best exponential fits' to absorbance–time traces collected by computer over 3—4 half-lives. However, many runs were checked for first-order behaviour by demonstrating linearity in semilog plots of $(A_\infty - A_t)$ *vs.* time. Plots of k_{obs} *vs.* coupler concentration were linear, passing through the origin. Variation in initial concentration of (1) over a four-fold range, holding coupler concentration constant and, in excess, had no effect on k_{obs}. Second-order rate constants, k_2, were obtained from $k_2 = k_{obs}/[C]_R$, where $[C]_R$ represents the concentration of the reactive form of the coupler.

Materials.—4′-Bis-(2-hydroxyethylamino)-2,4-diaminodiphenylamine was prepared by the following sequence of reactions. 1-Chloro-2,4-dinitrobenzene (10.1 g, 0.05 mol), *N,N*-bis-(2-hydroxyethyl)-p-phenylenediamine (17.7 g, 0.06 mol), and calcium carbonate (12 g) were heated with stirring in ethyl cellosolve (150 ml). When t.l.c. indicated exhaustion of starting materials, the mixture was poured onto ice. The precipitate was filtered off, washed three times with cold water, and dried *in vacuo* at 50 °C to yield crude 4′-bis-(2-hydroxyethylamino)-2,4-dinitrodiphenylamine (17.5 g). This product (2 g) was dissolved in ethyl acetate (150 ml) and reduced by Parr hydrogenation at 65 °C. The solution was filtered into a solution of hydrogen chloride in ethyl acetate; the resulting precipitate was filtered off, washed three times with ethyl acetate, and dried *in vacuo* to yield an off-white solid (0.3 g), m/z 302 (free base).

N,N-Bis-(2-hydroxyethyl)-p-phenylenediamine was prepared according to the method of Tong.[8] All other materials were commercially available.

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